REMARKS

Applicants thank the Examiner for consideration of the subject patent application. In the previous office action mailed November 8, 2007, Claims 81-84, 86, 98, 100, and 102-103 were pending. The applicants have canceled claims 98 and 100. Additionally, the Applicants have amended Claim 81. As such, Claims 81-84, 86 and 102-103 remain pending.

CLAIMS

Applicants have currently amended Claim 81 to recite a permeation enhancer of fatty acid esters of lactic acid. Support for the amendment can be found in original Claim 81 as well as page 23, lines 13-17; and page 24, lines 21-22. Additionally, Claim 81 has been amended to clarify the rubber-based pressure sensitive adhesive as including copolymers as found on page 36, line 9. Claims 98 and 100 have been canceled. As such, no new matter has been added.

Further, inasmuch as a permeation enhancer of fatty acid esters of lactic acid was previously recited as part of Claim 81, and is included within the species previously elected, the present amendment does not include any new matter outside the scope of previous Claim 81 which raises new issues or would require a new search.

35 U.S.C. § 112, first paragraph

Applicants have amended Claim 81 to clarify that the acrylate polymer includes homopolymers, copolymers, and terpolymers thereof as found on page 33, lines 20-21 of the specification and that the rubber-based pressure sensitive adhesive includes copolymers as found on page 36, line 9 of the specification. Additionally, Applicants have canceled claims 98 and 100 which

recite lauryl lactate. As such, Applicants submit that the pending claim set only contains material that is supported from the application and respectfully requests that the Examiner withdraw the present rejection.

35 U.S.C. § 103

The Examiner has rejected Claims 81-84, 86, 98, 100, and 102-103 under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 6,352,715 (hereinafter "'715"), Chinese Patent No. 1111987 (hereinafter "'987") and U.S. Patent No. 6,262,063 (hereinafter "'063").

The Applicant does not deem it necessary to recite the entire case law standard required in order to establish a *prima facie* case of obviousness. However, the Applicant would like to briefly remind the Examiner of the required three criteria for a *prima facie* case of obviousness, namely 1) that the asserted references as modified or combined must teach or suggest each and every element of the claimed invention, 2) that the asserted references as modified or combined must provide a sufficient likelihood of successfully making the modification or combination, and 3) that the Examiner must identify a reason for the modification or combination asserted. Nothing in the recent *KSR* Supreme Court case changes this basic analysis.

Specifically, the Examiner has rejected Claims 81-84, 86, 98, 100, and 102-103 as being obvious in view of two combinations: '715 in view of '063 and '987 in view of '063. As such a brief description of these references is provided below.

The '715 Reference

The '715 reference relates to a transdermal delivery system for Huperzine A. See Abstract. Generally, the '715 reference focuses on pH as a means to increase permeation of the drug and concludes that the only form of huperzine able to penetrate the skin is the neutral form. See col. 2, lines 65-67. The '715 reference further speculates that a possible method to further improve delivery of the neutral form of huperzine is to increase concentration of undissociated huperzine at the huperzine source, by adding non-polar solvents such as alcohols and glycols. See col. 8, lines 41-49. Such speculation also comes with the strong caution that, "However, these agents also reduce partitioning of drugs across the skin. Thus, various co-solvents need to be evaluated so as to achieve balance of satisfactory solubility and partitioning." See col. 8, lines 49-53.

The '987 Reference

As noted by the Examiner, the '987 reference is directed at a plaster containing Huperzine. See Abstract. Specifically, '987 mandates Azone (laurocapram) as a permeation enhancer. As noted by the Examiner, '987 does not teach the permeation enhancer presently claimed.

The '063 Reference

The '063 reference is directed at the treatment of tinnitus using muscurinic and/or opoid agents, preferably an anticholinesterase inhibitor, such as neoostigmine. See Abstract. The compositions are generally delivered as ear drops to the ear canal. See Examples. The '063 reference discloses numerous types of agent that may be used including 12 acetylcholinesterase inhibitors, one of which is Huperzine. See col. 2, lines 60-67 and col. 3, lines 1-4. The compositions can be administered in various regimes but are disclosed as being administered at least daily. See col. 4, lines

38-45. The '063 reference also discloses a laundry list of penetration enhancers including Azone and lauryl lactate. See col. 5, line 36 – col. 4, line 11.

The Examiner has argued that the present invention is obvious in view of either of the two primary references ('715 or '987) in view of the same secondary reference ('063). Specifically, the Examiner has stated that '715 does not provide the blood plasma levels of Huperzine. However, such blood plasma levels could be provided by one skilled in the art through manipulation of the system. The Examiner then combines the '715 reference with the '063 reference since the '063 reference allegedly teaches combining an enhancing agent with a drug to enhance the penetration of the drug including fatty acid esters.

Applicants contend that the '715 reference does not teach the presently recited blood levels, the fatty acid esters of lactic acid, or controlled release for at least 3 days from a single administration (see affidavit). The Examiner has alleged that the '715 reference suggests the use of co-solvents. However, the use of such co-solvents is clearly articulated as merely a mechanism to increase the concentration of undissociated huperzine in the huperzine source. Further, the '715 actually teaches away from indiscriminately adding co-solvents, as previously discussed. In other words, '715 explicitly states that such co-solvents need to be "evaluated" before adding as they can be detrimental to the efficacy of the system, i.e., they can reduce the partitioning coefficient. As such, '715 teaches away from the present combination asserted by the Examiner.

As the Applicant has raised the issue of teaching away, the Applicant would like to review the current case law regarding teaching away for the Examiner's convenience. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a prima facie case

of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Petersen, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a prima facie case of obviousness." (emphasis added) McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed. Cir. 2001). In identifying the appropriate standard for teaching away, the Court has further stated:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, **a reference will teach away if it suggests** that the **line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant." (emphasis added) In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Clearly in the present case, a person of ordinary skill in the art would be discouraged from interchanging co-solvents, including those of the '715 composition with those listed in the '063 reference, since the '715 reference specifically states that such co-solvents require an evaluation to ensure that the partitioning coefficient is not adversely effected.

The Applicants submits that such teachings regarding the fickle and unpredictable nature of penetration enhancers are generally known in the art. For example, U.S. Patent No. 5,500,222 also describes permeation enhancers in the same fashion:

> No "universal" permeation enhancer has been identified. Instead, the behavior of permeation enhancers is highly idiosyncratic; a permeation enhancer effective for one drug may not be effective with other drugs, including closely related drugs.
>
> Often, a permeation enhancer will exacerbate irritation and sensitization problems by allowing high transdermal permeation rates of the drug or permeation enhancer or permitting otherwise impermeable components of the transdermal device to enter the skin. Many potential permeation enhancers interact adversely with other components of transdermal devices. One major problem is that many

> potential permeation enhancers are not compatible with medically acceptable contact adhesives. Enhancers may improve the transdermal permeation rate adequately, but not adequately reduce the lag time.
>
> The use of a permeation enhancer in any transdermal drug delivery device necessarily complicates the design and development of the device. Permeation enhancers cause compatibility problems throughout the delivery system. Instead of having to characterize the properties of the reservoir compositions, adhesives, and release-controlling materials with respect to just the drug, these materials must now have the proper characteristics with respect to both the drug and the permeation enhancer. Typically, drugs and permeation enhancers have very different physical and chemical properties, and, in most cases, the properties of mixtures of the drug with the permeation enhancer are unknown. For example, permeation enhancers can cause, among other problems, cohesive failure of adhesives and can partition through other components in the system. See col. 2, line 47 through col. 3, line 12.

As such, Applicants submit that indiscriminately combining a transdermal system with a permeation enhancer is not taught in the art, and in fact, such a practice would not be expected to provide any likelihood of success based on the knowledge of permeation enhancer behavior currently known in the art.

Additionally, Applicants note that the Examiner is attempting to combine one possible permeation enhancer from a laundry list of permeation enhancers even though there is no motivation to choose any specific enhancer. In other words, Applicants submit that the one of ordinary skill in the art, upon reviewing the present combination of references, would have no reason to specifically select a fatty acid ester of lactic acid (out of the laundry list of enhancers) of the '063 reference and combine it with the transdermal system of the '715 reference. Therefore, Applicants contend that any such combination would necessarily be based on impermissible hindsight.

As the Applicant has raised the issue of hindsight analysis, the Applicant would like to review the current case law regarding hindsight analysis for the Examiner's convenience. The court has

stated that the Applicant's specification cannot be the basis for motivation, i.e., no hindsight reconstruction. Yamonouchi Pharmaceutical Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 56 U.S.P.Q.2d 1641(Fed. Cir.), reh'g denied, 2000 U.S. App. LEXIS 34047 (2000). Accordingly, if a prior art reference is sought to provide a specific element of a claim with the use of hindsight, any rejection based thereon is improper and should be withdrawn.

Furthermore, Applicants submit that the '715 reference does not provide a sustained release delivery of Huperzine based on the experimental results found by Applicants and further outlined in the Declaration section of the present response.

The Applicants submit that the present combination fails to teach each and every element of the present claim set, that there is no likelihood of success in making the present combination, and that there is no reason to make the specific combination based on the knowledge available in the art. As such, the Applicants submit that the Examiner has not made a *prima facie* case of obviousness and respectfully request that the Examiner withdraw the present rejection.

The Examiner has also combined the '987 reference with the '063 reference in rejecting the pending claim set. However, such a combination does not provide a likelihood of success and does not teach each and every element. Additionally, there is no apparent reason to make such a combination based on knowledge available in the art.

The Applicants renew the above arguments with respect to this combination. Specifically, based on the knowledge of permeation enhancer behavior (see above and U.S. Pat. No. 5,500,222), combining a permeation enhancer from a laundry list with a specific transdermal system would have no likelihood of success. Additionally, such a combination would be necessarily from hindsight as

neither reference (nor knowledge available from the art) could direct one skilled in the art, to specifically choose a fatty acid ester or lactic acid and combine it with the transdermal system of the '987 reference.

Additionally, the Applicants submit that, even if one skilled in the art would combine the '987 reference with the '063 reference, such a combination would require the use of Azone as a permeation enhancer since '987 explicitly mandates the use of Azone, alone or in a mixture, and Applicants have explicitly excluded Azone in the pending claim set. As such, the '987 reference, alone or in combination, cannot read on the present claim set.

Furthermore, the Applicants contend that the '987 transdermal system does not provide sustained release for 3 days. The Applicants direct the Examiner's attention to the Declaration previously submitted, which is also summarized in the Declaration section below.

The Applicants submit that the present combination fails to teach each and every element of the present claim set, that there is no likelihood of success in making the present combination, and that there is no reason to make the specific combination based on the knowledge available in the art. Additionally, the Applicants have excluded the required permeation enhancer cited in the primary reference, i.e., Azone. As such, the Applicants submit that the Examiner has not made a *prima facie* case of obviousness and respectfully request that the Examiner withdraw the present rejection.

Response to Arguments

The Examiner has alleged that the '715 reference and the '987 reference suggest permeation enhancers and that the '063 reference teaches the equivalency between fatty acids and their esters and azone in terms of skin enhancing effect, and this teaching would have motivated one skilled in the art

to include fatty acid esters in the transdermal delivery systems disclosed in '715 and '987. However, such a statement is misleading. The '063 reference does not teach any equivalency between the listed permeation enhancers, only that such compounds are generally known as permeation enhancers. However, as previously discussed, such knowledge is insufficient to establish that a specific enhancer is compatible with s specific system. As outlined in the '715 patent and further support in the art (also supported by the 5,500,222 patent), there is no universal permeation enhancer and that such enhancers cannot be indiscriminately combined or exchanged. Additionally, the Applicants submit that there is absolutely no reason one skilled in the art, upon reading the present references, would specifically select a fatty acid ester of lactic acid and combine such an enhancer with the transdermal systems of the '715 reference or the '987 reference. Furthermore, the Applicants submit that the explicit teaching of the '715 patent and knowledge available in the art would teach away from making such a combination. Also, Applicants submit that the '987 combination with '063 would result in a transdermal system that necessarily contains Azone which has been explicitly excluded from the present claims.

Response to Amendment

The Examiner has found the previously filed declaration as insufficient to overcome the present rejections for two reasons. First, the Examiner alleges that the present combinations teach the present invention and second, that the lauryl lactate used in the declaration is not disclosed by Applicants.

As to the first reason, Applicants submit that the present combinations do not support a case of *prima facie* obviousness as outlined in the above arguments. As to the second reason, in order to

advance prosecution, Applicants have amended the claim set to remove lauryl lactate. Claim 81 now recites fatty acid esters of lactic acid. As such, the declaration previously filed is specifically directed to a fatty acid ester of lactic acid, i.e., lauryl lactate. Lauryl lactate is well-known in the art to be a fatty acid ester of lactic acid and is a strong representative compound from this class of compounds.

As such, the Applicants submit that the previously filed declaration provides information pertinent to the present cited references and is commensurate with the scope of the pending claim set, and respectfully request that the Examiner consider such evidence.

DECLARATION

Applicants have submitted a declaration herewith that outlines the delivery results achieved by the huperzine patches of the '715 patent and the '987 patent. Following the teachings of the '715 patent, Applicants attempted to prepare a pH adjusted huperzine matrix patch as discussed therein. Immediately, it became apparent that the concept of adjusting pH is realistically limited to embodiments of the '715 patent which contain an aqueous component in the final formulation. In fact, as is scientifically well known, pH can only be measured for aqueous environments. Transdermal adhesive matrix patches generally do not contain significant, if any, moisture content, as drug is contained in an adhesive polymer which has been dried and laminated to a backing film. Nevertheless, following the protocols described in the attached declaration, Applicant attempted to create transdermal matrix patches with an adjusted pH as mentioned by the '715 patent.

The resultant patches had a very low flux rate. This is likely due to a phase separation encountered in the system during the attempt to make pH adjustment, see graph on Exhibit A. The

phase separation results in non-uniform patch contents which are simply incapable of delivering Huperzine at a rate required to achieve the serum level and duration elements required by the present invention. As further evidence of the inability of the '715 patent technology to provide sustained drug release for a significant period, Applicants have graphed Figure 11 of the '715 patent as daily delivery vs. time, as seen in Exhibit B. The conversion of this data into graphical form shows that the technology of the '715 patent had a daily delivery of drug decreasing linearly over a 7 day period, which also shows that the patch is not designed for sustained delivery, but for immediate release purposes as the linear decrease shows that delivery is not "sustained".

Applicants also tested the Azone patch of the '987 patent. The results of the Azone patch are shown in Exhibit C. The graph clearly shows that the Azone patch has a large initial spike of drug delivery followed by a very rapid decrease. The flux pattern is indicative of Azone's nature to destroy skin layers resulting in an uncontrolled release of huperzine. The amount of huperzine delivered cannot be controlled with Azone as the enhancer and as shown, the delivery rate far exceeds the target levels for the present invention, as well as the safety levels for huperzine. Therefore, effective sustained delivery of huperzine cannot be achieved with the Azone patch.

Therefore, Applicants submit that neither the '715 patent nor the '987 patent teach a huperzine adhesive matrix patch having a permeation enhancer capable of controlled release over at least a three day period. Therefore, the Applicants submit that the currently amended claims are patentable over the '715 patent and the '987 patent, and respectfully request allowance.

CONCLUSION

If any impediment remains to further examination of the present application after consideration of the above-recited election and remarks, which could be removed during a telephone interview, the Examiner is invited to telephone the undersigned attorney at (801) 566-6633 so that such issues may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 20-0100.

DATED this 8th day of January, 2008.

Respectfully submitted,

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